Contains Nonbinding Recommendations

Draft Guidance on Dexmethylphenidate Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Dexmethylphenidate Hydrochloride

Form/Route: Capsule, Extended Release; Oral

Recommended studies: 3 Studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 40 mg
   Subjects: Healthy males and non-pregnant females, general population
   Additional Comments:

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2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 40 mg
   Subjects: Healthy males and non-pregnant females, general population
   Additional Comments: Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

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3. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 40 mg
   Subjects: Healthy males and non-pregnant females, general population
   Additional Comments: Fasting study, with contents sprinkled over a spoonful of applesauce in accordance with the approved labeling of the RLD.

Analytes to measure (in appropriate biological fluid): Dexmethylphenidate in plasma

Bioequivalence based on (90% CI): Dexmethylphenidate
Please refer to Additional Comments below for more guidance regarding bioequivalence.

Waiver request of in-vivo testing: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, and 35 mg based on (i) acceptable bioequivalence studies on the 40 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in-vivo testing.[1]

[1]CFR § 320.24(b)(6)

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional in vitro dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

> Testing Conditions: 900 mL, 0.1N HCl, USP apparatus I (basket) at 100 rpm, with and without alcohol;
>
> Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours
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> Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours
>
> Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours
>
> Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Both test and reference listed drug (RLD) products should be tested accordingly and data should be provided on individual unit, means, range and %CV on all strengths.

Additional comments:

The Focalin^{TM} XR Capsule labeling states that "Focalin XR (dexmethylphenidate hydrochloride) extended-release capsule is an extended-release formulation of dexmethylphenidate with a bi-modal release profile. Each bead-filled Focalin XR capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of dexmethylphenidate and a second delayed release of dexmethylphenidate."

Thus, Focalin^{TM} XR is a multiphasic modified-release formulation designed to release a bolus of dexmethylphenidate followed by slower delivery later in the day. According to the FDA-approved labeling for this product, clinical studies showed statistically significant improvement in behavioral assessment scores throughout the day, relative to placebo, following administration of a single morning dose. As this multiphasic modified-release dosage form is designed to achieve both rapid onset of activity and sustained activity throughout the day, FDA suggests that additional bioequivalence metrics may be appropriate to ensure that a generic (test) version is therapeutically equivalent to the corresponding reference product. Thus, for Focalin^{TM} XR the following two pAUC metrics are proposed in addition to the traditional (AUC_{∞} and C_{max}) metrics:

- $AUC_{0\text{-}T}$ should compare test & reference systemic exposure responsible for early onset of response during the early part of the once-daily dosing interval; and
- $AUC_{T\text{-}t}$ should compare test & reference systemic exposure responsible for sustaining the response later during the once-daily dosing interval.

The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the above four C_{max} and AUC metrics (C_{max}, $AUC_{0\text{-}T}$, $AUC_{T\text{-}t}$, AUC_{∞}) should fall within the limits of 80-125%.

The sampling time (T) for the first pAUC is based on time at which 90-95% of subjects are likely to achieve optimal early onset of response. Because the rate of initial methylphenidate absorption is associated with the rate of early onset of response, the sampling time "T" is determined based on T_{max} of the immediate-release portion of the formulation. T_{max} is a pharmacokinetic parameter associated with rate of response.

Fasting Study and Fasting (capsule compared to RLD, sprinkled on a spoonful of applesauce) Study: Log-transformed $AUC_{0\text{-}2.5}$, $AUC_{2.5\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}, where $AUC_{0\text{-}2.5}$ is the area under the plasma-concentration vs. time curve from 0 to 2.5 hours, $AUC_{2.5\text{-}t}$ is area under the curve from 2.5 hours to the last measurable time point; $AUC_{0\text{-}\infty}$ is area under the curve from 0 to infinity, and C_{max} is the maximum plasma concentration. The partial AUCs, $AUC_{0\text{-}2.5}$ and $AUC_{2.5\text{-}t}$, have been determined to be the most appropriate parameters for evaluation of the drug bioavailability responsible for the quick onset and sustained maintenance of the clinical response throughout the 24 hr dosing period. These two partial AUCs (pAUCs) replace the usual $AUC_{0\text{-}t}$, and together with the other bioequivalence parameters, $AUC_{0\text{-}\infty}$ and Cmax, will ensure that the pharmacokinetic profiles and clinical effects of test and reference products are sufficiently similar.

Fed Study: Log-transformed $AUC_{0\text{-}3.5}$, $AUC_{3.5\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}, where $AUC_{0\text{-}3.5}$ is the area under the plasma-concentration vs. time curve from 0 to 3.5 hours, $AUC_{3.5\text{-}t}$ is area under the curve from 3.5 hours to the last measurable time point; $AUC_{0\text{-}\infty}$ is area under the curve from 0 to infinity, and Cmax is the maximum plasma concentration. The partial AUCs, $AUC_{0\text{-}3.5}$ and $AUC_{3.5\text{-}t}$, have been determined to be the most appropriate parameters for evaluation of the drug bioavailability responsible for the quick onset and sustained maintenance of the clinical response throughout the 24 hr dosing period.[1] These two pAUCs replace the usual $AUC_{0\text{-}t}$, and together with the other bioequivalence parameters, $AUC_{0\text{-}\infty}$ and C_{max}, will ensure that the pharmacokinetic profiles and clinical effects of test and reference products are sufficiently similar.

The reasons for selecting 2.5 hours and 3.5 hours, respectively, for the partial AUCs in fasting and fed studies are as follows:

- For the immediate-release portion of the formulation, T_{max} is about 1.5 hours in fasting subjects;
- Food prolongs the T_{max} of immediate-release methylphenidate by about 1 hour;
- The IR methylphenidate T_{max} standard deviation is about 0.5 hour;
- For T_{max}, two standard deviations = 1.0;
- Generally, approximately 95% of observations fall within two standard deviations of the mean;

Thus, since the T_{max} from the immediate-release portion of this formulation is about 1.5 hours under fasting conditions and 2.5 hours under fed conditions, partial AUCs calculated to 0-2.5 hours in fasting and sprinkling BE studies and 0-3.5 hours in a fed BE study should capture the responses of 95% of the subjects. This should provide additional assurance that a test and reference product will be therapeutically equivalent over the early part of the daily dosing interval, corresponding to onset of response. Likewise, $AUC_{2.5\text{-}t}$ and $AUC_{3.5\text{-}t}$, to be used in fasting and fed BE studies, respectively, should ensure that two products are therapeutically equivalent over the later part of the daily dosing interval, corresponding to the duration of the sustained response.